Dwell time of a Brownian interacting molecule in a cellular microdomain

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Abstract

The time spent by an interacting Brownian molecule inside a bounded microdomain has many applications in cellular biology, because the number of bounds is a quantitative signal, which can initiate a cascade of chemical reactions and thus has physiological consequences. In the present article, we propose to estimate the mean time spent by a Brownian molecule inside a microdomain Ω which contains small holes on the boundary and agonist molecules located inside. We found that the mean time depends on several parameters such as the backward binding rate (with the agonist molecules), the mean escape time from the microdomain and the mean time a molecule reaches the binding sites (forward binding rate). In addition, we estimate the mean and the variance of the number of bounds made by a molecule before it exits Ω. These estimates rely on a boundary layer analysis of a conditional mean first passage time, solution of a singular partial differential equation. In particular, we apply the present results to obtain an estimate of the mean time spent (Dwell time) by a Brownian receptor inside a synaptic domain, when it moves freely by lateral diffusion on the surface of a neuron and interacts locally with scaffolding molecules.

1 Introduction

Biochemical reactions in cellular microdomains involve, in general, a small number of molecules that can bind to agonist molecules, confined in some

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subregions. A microdomain Ω is defined as a bounded domain where a large fraction of the boundary $\partial\Omega_r$ is reflective and a small part $\partial\Omega_a$ of it is absorptive, which allows molecules to enter or/and exit. Under normal physiological conditions, a molecule can be trapped inside a microdomain for a period long enough, compared to other time scales such as free diffusion or binding time. Because a molecule can be trapped for a long time, many chemical bounds can be made, before it exits. From a physiological stand point, an interesting property of such microdomain is that depending on the number of chemical bounds made by a molecule, a cascade of chemical reactions can be initiated, which ultimately affects some physiological properties. Our interest here is to estimate the number of chemical bounds made by a Brownian interacting molecule inside Ω. This number depends on the geometry of the microdomain and the distribution of agonist molecules. We also provide an estimation of the mean time spent (Dwell time) by a molecule inside the microdomain, denoted by $E(\tau_D)$. For that purpose, we derive an asymptotic formula for the Dwell time, the mean and the variance of the number of bounds made before the molecule exits, as the ratio $\frac{|\partial\Omega_a|}{|\partial\Omega_r|}$ tends to zero. Finally, we derive a formula for the Dwell time of a molecule inside Ω, when a steady state flux of molecules is maintained fixed at the absorbing boundary. The role of the flux is to fix the number of free binding sites. Using the present method, we also obtain an estimate of the forward binding rate constant. Historically, the theory of chemical reactions at a molecular level limited by diffusion has been developed by many authors, to quote but a few [1, 2, 3, 4, 5]: using the classical theory of diffusion and interactions with binding sites, various rate constants were computed. Recently, using averaged equations, chemical reactions in microdomains have been described in [6, 7]. Chemical reactions in closed microdomains were studied in [8], where we obtain, in particular, some estimates on the mean of the variance of the number of bound molecules in a steady state regime. In [9], an asymptotic estimate of the mean time it takes for a Brownian molecule to escape an empty domain through small openings located on the boundary, was obtained using a new type of singular perturbation problem. More specifically, if D denotes the diffusion constant, $|\Omega|$ the volume of the domain Ω and $\varepsilon = \frac{|\partial\Omega_a|}{|\partial\Omega|} << 1$ is the ratio of the absorbing to the total boundary, then for ε small, the leading order term of the mean escape time $\tau(\boldsymbol{x})$ (for a molecule starting at position $\boldsymbol{x}$, far from the entrance) is given by

$$\tau(\boldsymbol{x}) = \frac{|\Omega|}{\pi D}\log(\frac{1}{\varepsilon}) + O(1). \tag{1.1}$$

In the first approximation, the mean time $\tau(\boldsymbol{x})$ does not depend on the initial position $\boldsymbol{x}$ and will be denoted by τ. In this article, we obtain an explicit asymptotic estimation of the Dwell time $E(\tau_D)$ as a function of the characteristic sizes of the domain Ω, the size of the small openings $\partial\Omega_a$, the number of the binding molecules. More specifically, $E(\tau_D)$ is given by expression (2.12),

which depends on the mean time $\langle \tau \rangle$ to exit when no binding occurs, the mean time $\langle T \rangle$ to enter into the binding site area, m_δ the mean probability to bind before exit and the backward binding rate k_{-1}. We get

$$E(\tau_D) = \langle \tau \rangle + \frac{1 - m_\delta}{m_\delta} \left(\langle T \rangle + \frac{1}{k_{-1}} \right). \tag{1.2}$$

It is well known from the theory of chemical reactions that the backward binding rate k_{-1} depends only on the local interactions between two interacting molecules. If ΔE denotes the activation barrier, kT_e is the energy due to the temperature, the Arrhenius law states that:

$$k_{-1} = Ce^{-\frac{\Delta E}{kT_e}}, \tag{1.3}$$

where C is a constant that depends on the temperature T_e, the electrostatic potential barrier ΔE generated by the binding molecule and the friction coefficient [10]. In the first part of the paper, we derive equation (1.2) by counting the number of bounds between the Brownian molecule and the agonist molecules, before the Brownian molecule exits the domain. In the second part, we derive some asymptotic estimates of the quantities $\langle T \rangle$, $\langle \tau \rangle$ and m_δ as a function of the geometry, when the radius δ of the binding site tends to zero. Although the present computations are carried out in two dimensions, they can be extended to dimension 3 by using the techniques developed in [11]. Finally in the last part, we apply the present computations to study chemical reactions occurring in synaptic microdomains: the chemical reactions are the binding of receptors with the scaffolding molecules. It is indeed of great interest to analyze the mechanism that regulates the number and the type of receptors at a synapse, because receptors control the synaptic weight. Any fluctuations of the number results in a variation of the synaptic weight and affects the reliability of the synaptic transmission. Moreover, certain experimental protocols have lead to a Long Term Potentiation of a synapse, a mechanism which is associated with a change of the number and the type of certain receptors [12, 13]. The regulation of synaptic plasticity is a fundamental process underlying learning and memory [12, 13] and recently, single molecule tracking has revealed that the number of postsynaptic receptors, which participate to the synaptic transmission, is not fixed but it changes due to constant traffick of receptors on the surface of neurons. Receptors move in and out from synaptic regions [14] [15] and following these observations, many questions have been raised: in particular, what determines the time spent by a receptor inside a synapse? How receptors can be stabilized inside a synapse? How long they stay inside synaptic microdomains? Such questions are partially answered in the present paper. In particular, our computation of the Dwell time of a receptor inside a specific microdomain, called the Postsynaptic density (PSD) takes into account the interaction with the scaffolding molecules, which was ignored in [9].

1.1 Molecular dynamics in a microdomain

The dynamics of a molecule or a protein moving on the surface of a cell is usually described in the Smoluchowsky limit (large friction) of the Langevin equation [10]: for a molecule of mass m, described by its position X at time t, with a friction coefficient γ, moving inside a potential well V, the Smoluchowsky limit of the Langevin equation is

$$\gamma \dot{X} + \nabla V(X) = \sqrt{2\gamma\varepsilon_e}\dot{w}, \tag{1.4}$$

where $\varepsilon_e = \frac{kT_e}{m}$ and w is a Gaussian random variable with variance 1 and mean 0. In a microdomain Ω, where a large fraction of the boundary is reflective $\partial\Omega_r$ and a small part of it is absorptive $\partial\Omega_a$, the probability density function (pdf) p to find X at time t in the surface element $\boldsymbol{x} + d\boldsymbol{x}$ satisfies the Fokker-Planck Equation (FPE)

$$\frac{\partial p(\boldsymbol{x},t)}{\partial t} = D\Delta p(\boldsymbol{x},t) - \nabla\cdot(\nabla V(\boldsymbol{x})p(\boldsymbol{x},t)) \text{ for } \boldsymbol{x}\in\Omega \tag{1.5}$$

$$\boldsymbol{J}(\boldsymbol{x},t)\cdot\boldsymbol{n} = 0 \text{ for } \boldsymbol{x}\in\partial\Omega_r \tag{1.6}$$

$$p(\boldsymbol{x},t) = 0 \text{ for } \boldsymbol{x}\in\partial\Omega_a \tag{1.7}$$

where $D = \gamma\varepsilon_e$ is the diffusion constant, $\boldsymbol{n}$ is the external normal at the boundary, the flux $\boldsymbol{J}$ is given by

$$\boldsymbol{J}(\boldsymbol{x},t) = -D\nabla p(\boldsymbol{x},t) + \nabla V(\boldsymbol{x})p(\boldsymbol{x},t). \tag{1.8}$$

We denote by t^x the first time the molecule arrives at the absorbing boundary $\partial\Omega_a$, when it started at position $\boldsymbol{x}$. It is well known [10] that the mean first passage is the expectation of the time t^x and is given by

$$\begin{aligned} E^{\boldsymbol{x}}(t^x) &= \int_0^\infty t\frac{d}{dt}Pr\{t^x < t\}dt = \int_0^\infty Pr\{t^x > t\}dt \\ &= \int_0^\infty\int_\Omega p(\boldsymbol{y},t|\boldsymbol{x})d\boldsymbol{y}dt, \end{aligned}$$

where $p(\boldsymbol{y},t|\boldsymbol{x})$ is the pdf of the process X, conditioned on the initial position $\boldsymbol{x}$, that is, as t goes to zero,

$$p(\boldsymbol{y},t|\boldsymbol{x}) \to \delta(\boldsymbol{x}-\boldsymbol{y}), \tag{1.9}$$

where δ is the Delta-Dirac function. In equation (1.5), V represents the potential wells generated by the binding molecules inside the domain Ω. It is, in fact, the sum of the local potential wells, supported inside a ball of finite radius

generated by the binding molecules. Usually the binding molecules are scattered inside the domain Ω, but in the present model we replace the scattered distribution of binding molecules by a simplified distribution, where we imagine that all the binding molecules are located inside a compartment $D(\delta)$ in Ω. In the present description, the potential V becomes an effective potential defined in $D(\delta)$, whose characteristics should be such that the classical chemical reaction theory is recovered. More specifically, we can define the microdomain Ω containing the binding domain $D(\delta)$, which replaces the domain with many scattered binding sites: this simplified domain made of two compartments is called the homogenized microdomain and is described as (see figure 1)

1. An internal compartment, which is described as a disk $D(\delta)$ of radius δ. This disk represents the region where the binding sites are located. Instead of using the dynamics associated with equation (1.4), we describe the entrance and the exit of a molecule inside $D(\delta)$ using a Poissonnian description, where the mean can be related to the properties of the potential well. For that purpose, we recall that a chemical reaction with a binding molecule is described as the arrival of a Brownian molecule inside the disk $D(\delta)$. The release process is modeled as the escape of the molecule from the potential well V and is described by the chemical reaction

$$R + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} RS \tag{1.10}$$

   where $\frac{1}{k_{-1}}$ is the mean binding time and depends only on the local potential well, generated by the binding molecules [16] [10].

2. An external compartment separated from the rest of the biological environment by the boundary $\partial\Omega_r$, containing small openings $\partial\Omega_a$. Molecules can enter or exit through the openings and thus can be exchanged with the rest of the cellular medium (see figure 1). The dynamics of a molecule in that compartment is described as pure Brownian until it escapes.

1.2 Time spent by a molecule inside a disk containing a small opening

We estimate asymptotically the Dwell time $E(\tau_D)$ of a molecule inside a domain Ω, when the domain Ω is a disk $D(R)$ of radius R. The case of a general domain is left open. By definition, $E(\tau_D)$ is the mean time to exit, averaged over an initial uniform distribution. We make the following assumptions: the ratio ε of

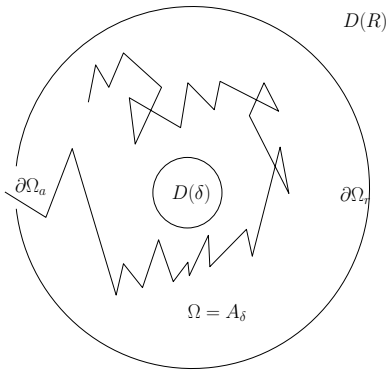

Figure 1: Model of a cellular microdomain in two dimensions. The domain is a disk $D(R)$ of radius R, made of two compartments: an inner disk $D(\delta)$ of radius δ and the annulus $A_\delta = D(R) - D(\delta)$. A molecule moves by Brownian motion inside A_δ until it hits $D(\delta)$ or the absorbing boundary $\partial\Omega_a$. When the Brownian molecule enters into $D(\delta)$, which represents the domain of chemical reactions, while it reacts with an effective binding molecule during a mean time (the inverse of the backward binding rate) its movement in $D(\delta)$ is frozen. The molecule is then released uniformly inside the annulus $A_\delta = D(R) - D(\delta)$. This scenario repeats until the molecule hits the absorbing boundary $\partial\Omega_a$, where the molecule is finally removed.

the absorbing to the reflective boundary of $D(R)$ is small $<< 1$. The absorbing (resp. reflecting) part is denoted $\partial\Omega_a$ (resp. $\partial\Omega_r$). The computation of the Dwell time will be made using the homogenization version of the domain, described in the previous paragraph: the binding molecules are located in the small concentric disk D(δ), where $\delta << R$. Each time a molecule enters into D(δ), it can be bound with a binding molecule and will be released in the annulus $A_\delta(R) = D(R) - D(\delta)$. Since R is a fixed parameter, we will denote the annulus by A_δ. We assume that the boundary $\partial D(\delta)$ is always absorbing.

2 The Dwell Time $E(\tau_D)$

The goal of this section is to derive a general expression of the Dwell time $E(\tau_D)$. The movement of a molecule is described here as Brownian (see [17, 14] for the case of a synapse) with a diffusion constant D and $X^{\boldsymbol{x}}(t)$ is the position of a molecule at time t starting at position $\boldsymbol{x}$. $E(\tau_D)$ is the mean time a molecule remains inside the domain Ω before it exits, averaged over a uniform initial distribution inside the annulus $A_\delta = D(R) - D(\delta)$. Inside A_δ, a molecule diffuses freely until it hits $\partial D(\delta)$. Inside $D(\delta)$, a bound molecule is kept fixed for a mean time $\frac{1}{k_{-1}}$, before being released inside A_δ at a random position, distributed uniformly. To estimate the Dwell time $E(\tau_D)$, we first consider the

Dwell time $E(\tau^{\boldsymbol{x}})$, conditioned on the initial position located inside A_δ. We do not consider here the entrance of the Brownian receptor inside the domain, which would require to use a Langevin formulation of the dynamics [10]. We derive a formula for $E(\tau^{\boldsymbol{x}})$ by counting the number of times a molecule enters into $D(\delta)$ before it exits: either a molecule exits with no bindings or many bindings occur, before the receptor leaves $D(R)$. Let $T^A_{\boldsymbol{x}}$ denote the first passage time the trajectory $X^{\boldsymbol{x}}(t)$ hits the absorbing boundary $\partial\Omega_a$. Similarly we define by $T^S_{\boldsymbol{x}}$ the first passage time of the trajectory $X^{\boldsymbol{x}}(t)$ to the boundary of $D(\delta)$. We define now the probability $p_\delta(\boldsymbol{x})$ that a trajectory $X^{\boldsymbol{x}}(t)$ leaves the domain A_δ before any bounds occur, explicitly

$$p_\delta(\boldsymbol{x}) = \Pr\{T^A_{\boldsymbol{x}} < T^S_{\boldsymbol{x}}\}. \tag{2.1}$$

2.1 The general formula for the mean Dwell time $E(\tau_D)$

To estimate $E(\tau_D)$, we consider the different random events related to the number of times the Brownian molecule enters into the region A_δ, before it exits. $F_0^{\boldsymbol{x}}$ is the event that a receptor exits the microdomain A_δ when no bindings occur, starting at position $\boldsymbol{x}$. $F_1^{\boldsymbol{x}}$ is the event that a receptor starting at $\boldsymbol{x}$, enters the domain $D(\delta)$ only once and then exits without entering again in $D(\delta)$. Similarly, we define the event $F_n^{\boldsymbol{x}}$ that a receptor starting at position $\boldsymbol{x}$ exits after exactly n bounds. The probability that the molecule has left the domain before time t is $Pr\{\tau^{\boldsymbol{x}} < t\}$. The mean time is given by

$$\begin{aligned} E(\tau^{\boldsymbol{x}}) &= \int_0^\infty t\frac{d}{dt}Pr\{\tau^{\boldsymbol{x}} < t\}dt & (2.2)\\ &= \sum_n \int_0^\infty t\frac{d}{dt}Pr\{\tau^{\boldsymbol{x}} < t, F_n^{\boldsymbol{x}}\}dt. & (2.3)\end{aligned}$$

We use Bayes formula to get

$$E(\tau^{\boldsymbol{x}}) = E(\tau^{\boldsymbol{x}}|F_0^{\boldsymbol{x}})\Pr(F_0^{\boldsymbol{x}}) + E(\tau^x|F_1^{\boldsymbol{x}})\Pr(F_1^{\boldsymbol{x}}) + E(\tau^{\boldsymbol{x}}|F_2^{\boldsymbol{x}})\Pr(F_2^{\boldsymbol{x}}) + ... \tag{2.4}$$

where

$$E(\tau^{\boldsymbol{x}}|F_n^{\boldsymbol{x}}) = \int_0^\infty t\frac{d}{dt}Pr\{\tau^{\boldsymbol{x}} < t|F_n^{\boldsymbol{x}}\}dt. \tag{2.5}$$

$Pr\{\tau^{\boldsymbol{x}} < t|F_n^{\boldsymbol{x}}\}$ is the probability that $\tau^{\boldsymbol{x}} < t$ conditioned to the event that exactly n bounds are made before the molecule exits the domain $D(R)$. When a molecule detaches from the domain $D(\delta)$, in this model, it is released inside the domain A_δ according to a density distribution $\rho(\boldsymbol{x})$: immediately after the mean duration $\frac{1}{k_{-1}}$, the molecule is released inside the volume element $\boldsymbol{x} + d\boldsymbol{x}$

with a probability $\rho(\boldsymbol{x})d\boldsymbol{x}$. To compute the first term in equation (2.4), we notice that

$$E(\tau^x|F_0^{\boldsymbol{x}})\Pr(F_0^{\boldsymbol{x}}) = E(T_{\boldsymbol{x}}^A|T_{\boldsymbol{x}}^A < T_{\boldsymbol{x}}^S)p_\delta(\boldsymbol{x}). \tag{2.6}$$

The second term $E(\tau^{\boldsymbol{x}}|F_1^{\boldsymbol{x}})\Pr(F_1^{\boldsymbol{x}})$ is the sum of two terms. First the mean time it takes for a molecule to reach the boundary $\partial D(\delta)$ and stays there for a mean time $\frac{1}{k_{-1}}$ and second the mean time to go from a point $\boldsymbol{x}_1$, where the molecule starts afresh, to the absorbing boundary. If we note that the probability to reach $\partial D(\delta)$ before $\partial\Omega_a$ starting from $\boldsymbol{x}$ is $1 - p_\delta(\boldsymbol{x})$, then we have:

$$E(\tau^{\boldsymbol{x}}|F_1^{\boldsymbol{x}})\Pr(F_1^{\boldsymbol{x}}) = (1-p_\delta(\boldsymbol{x}))\times$$
$$\left((E\{T_{\boldsymbol{x}}^S|T_{\boldsymbol{x}}^S < T_{\boldsymbol{x}}^A\} + \frac{1}{k_{-1}})\int_{A_\delta}\rho(\boldsymbol{x}_1)p_\delta(\boldsymbol{x}_1)d\boldsymbol{x}_1 + \int_{A_\delta}E\{T_{\boldsymbol{x}_1}^A|T_{\boldsymbol{x}_1}^A < T_{\boldsymbol{x}_1}^S\}\rho(\boldsymbol{x}_1)p_\delta(\boldsymbol{x}_1)d\boldsymbol{x}_1\right).$$

Similarly, the general term where exactly k bounds are formed is computed, with the notation

$$t^A(\boldsymbol{x}) = E\{T_{\boldsymbol{x}}^A|T_{\boldsymbol{x}}^A < T_{\boldsymbol{x}}^S\} \tag{2.7}$$

$$t^S(\boldsymbol{x}) = E\{T_{\boldsymbol{x}}^S|T_{\boldsymbol{x}}^S < T_{\boldsymbol{x}}^A\}. \tag{2.8}$$

We get,

$$\begin{aligned}
E(\tau^{\boldsymbol{x}}|F_n^{\boldsymbol{x}})\Pr(F_n^{\boldsymbol{x}}) &= \int_{A_\delta}\ldots\int_{A_\delta}\left(\sum_{i=0}^{n-1}t^S(\boldsymbol{x}_i) + \frac{n}{k_{-1}} + t^A(\boldsymbol{x}_n)\right)\\
&\quad \prod_{i=1}^{n-1}(1-p_\delta(\boldsymbol{x}_i))\rho(\boldsymbol{x}_i)(1-p_\delta(\boldsymbol{x}))p_\delta(\boldsymbol{x}_n)\rho(\boldsymbol{x}_n)d\boldsymbol{x}_1\ldots d\boldsymbol{x}_n.\\
&= (1-p_\delta(\boldsymbol{x}))\Big\{t^S(\boldsymbol{x})(1-m_\delta)^{n-1}m_\delta\\
&+ (n-1)(1-m_\delta)^{n-2}m_\delta\int_{A_\delta}t^S(\boldsymbol{y})(\rho(\boldsymbol{y}) - p_\delta(\boldsymbol{y})\rho(\boldsymbol{y}))d\boldsymbol{y}\\
&+ \frac{n}{k_{-1}}(1-m_\delta)^{n-1}m_\delta + (1-m_\delta)^{n-1}\int_{A_\delta}t^A(\boldsymbol{y})p_\delta(\boldsymbol{y})\rho(\boldsymbol{y})d\boldsymbol{y}\Big\}
\end{aligned}$$

where

$$m_\delta = \int_{A_\delta}p_\delta(\boldsymbol{y})\rho(\boldsymbol{y})d\boldsymbol{y}.$$

Formula (2.4) is in fact a geometric sum and using the generic expression of the series, we get

$$\begin{aligned}
E(\tau^{\boldsymbol{x}}) &= t^A(\boldsymbol{x})p_\delta(\boldsymbol{x}) + \frac{1-p_\delta(\boldsymbol{x})}{m_\delta}\Big\{t^S(\boldsymbol{x}) + \int_{A_\delta}t^A(\boldsymbol{y})p_\delta(\boldsymbol{y})\rho(\boldsymbol{y})d\boldsymbol{y} \qquad (2.9)\\
&+ \frac{1}{m_\delta}(\int_{A_\delta}t^S(y)(\rho(\boldsymbol{y}) - p_\delta(\boldsymbol{y})\rho(\boldsymbol{y}))d\boldsymbol{y} + \frac{1}{k_{-1}})\Big\}.
\end{aligned}$$

When ρ is uniformly distributed, formula (2.9) can be simplified. Using that

$$m_\delta = \frac{1}{|A_\delta|}\int_{A_\delta} p_\delta(\boldsymbol{y})d\boldsymbol{y},$$

where $|A_\delta|$ is the volume of A_δ and if we define the two mean times

$$\langle\tau\rangle = \frac{\int_{A_\delta} t^A(\boldsymbol{x})p_\delta(\boldsymbol{x})d\boldsymbol{x}}{\int_{A_\delta} p_\delta(\boldsymbol{y})d\boldsymbol{y}} \tag{2.10}$$

and

$$\langle T\rangle = \frac{\int_{A_\delta} t^S(\boldsymbol{x})(1-p_\delta(\boldsymbol{x}))d\boldsymbol{x}}{\int_{A_\delta}(1-p_\delta(\boldsymbol{y}))d\boldsymbol{y}}, \tag{2.11}$$

then the Dwell time $E(\tau_D)$ is given by the average of $E(\tau^{\boldsymbol{x}})$ with respect to the uniform distribution and we get

$$E(\tau_D) = \langle\tau\rangle + \frac{1-m_\delta}{m_\delta}\left(\langle T\rangle + \frac{1}{k_{-1}}\right). \tag{2.12}$$

In the next paragraphs we obtain an explicit asymptotic estimate of for component of formula (2.12).

Remark. It seems artificial to free a bounded molecule not immediately at the boundary of the domain D_δ. But in fact, the release process can be modeled by re-initiating the molecule at the boundary of D_δ, otherwise it would immediately return to a bounded state. To avoid this unrealistic behavior, we have used the distribution function $\rho(\boldsymbol{y})$ to model the releasing process. A more accurate scenario would require to use a Langevin description, which accounts for the acceleration of the molecule: when a molecule is released with a random Gaussian initial velocity, it can travel up to a certain distance, before its velocity reaches the value of mean thermal velocity of free molecules.

2.2 The mean number of bounds before exit

To estimate the mean number of bounds made by a molecule before it exits, we use the analysis of the previous paragraph. The probability that a molecule starting at $\boldsymbol{x}$ does not bind before exit is exactly $\Pr(F_0^{\boldsymbol{x}})$, while the probability that exactly k bounds are made is $\Pr(F_k^{\boldsymbol{x}})$. We define the average probability by

$$\Pr(F_k) = \int_{A_\delta} \Pr(F_k^{\boldsymbol{x}})\rho(\boldsymbol{x})d\boldsymbol{x}.$$

The probability $\Pr(F_k^{\boldsymbol{x}})$ can be expressed in terms of the conditional probability p as follows

$$\Pr(F_1^{\boldsymbol{x}}) = \int_{A_\delta} p_\delta(\boldsymbol{y})\rho(\boldsymbol{y})d\boldsymbol{y}(1 - p_\delta(\boldsymbol{x}))$$

and the average probability $\Pr(F_1)$ is given by

$$\Pr(F_1) = \int_{A_\delta} \rho(\boldsymbol{x}) \Pr(F_1^{\boldsymbol{x}})d\boldsymbol{x} = \int_{A_\delta}\int_{A_\delta} p_\delta(\boldsymbol{y})\rho(\boldsymbol{y})d\boldsymbol{y}\rho(\boldsymbol{x})(1 - p_\delta(\boldsymbol{x}))d\boldsymbol{x} = m_\delta(1 - m_\delta).$$

More generally,

$$\Pr(F_k) = \int_{A_\delta} ... \int_{A_\delta} p_\delta(\boldsymbol{y}_k)\rho(\boldsymbol{y}_k)d\boldsymbol{y}_k(p_\delta(\boldsymbol{y}_{k-1})\rho(\boldsymbol{y}_{k-1})dy_{k-1})...(1 - p_\delta(\boldsymbol{y}_1))\rho(\boldsymbol{y}_1)d\boldsymbol{y}_1(1 - p_\delta(\boldsymbol{x}))$$

and after some integrations we get

$$\Pr(F_k) = m_\delta(1 - m_\delta)^k.$$

The mean M_b and the variance V_b of the number of bounds before exit are given by the well known formula of geometric probability,

$$\begin{aligned} M_b &= \sum k \Pr(F_k) = \sum k m_\delta(1 - m_\delta)^k \\ &= \frac{1 - m_\delta}{m_\delta} = \frac{\int_{A_\delta}(1 - p_\delta(\boldsymbol{y}))d\boldsymbol{y}}{\int_{A_\delta} p_\delta(\boldsymbol{y})d\boldsymbol{y}} \qquad (2.13) \\ V_b &= \sum k^2 \Pr(F_k) - (\sum k \Pr(F_k))^2 = \left(\frac{1 - m_\delta}{m_\delta^2}\right). \qquad (2.14) \end{aligned}$$

Later on we will give an asymptotic expansion of m_δ, V_b and M_b as a function of the parameter δ.

3 Estimation of the probability $p_\delta(x) = Pr\{T_{\boldsymbol{x}}^a < T_{\boldsymbol{x}}^S\}$.

To obtain an asymptotic expansion of the probability $p_\delta(x)$ that a molecule exits before it enters into the domain $D(\delta)$, that is, before it binds to any binding sites, we use the notations of the previous section. T_x^a denotes the first time a molecule starting from x hits the absorbing boundary. We assume that when a molecule exits the domain Ω, it does not come back. T_x^S is the first time a molecule hits the inner circle $\partial D(\delta)$. The probability $q_\delta(\boldsymbol{x}) =$

$1 - p_\delta(\boldsymbol{x}) = \Pr\{T^S_{\boldsymbol{x}} < T^a_{\boldsymbol{x}}\}$ of the event $T^a_{\boldsymbol{x}} > T^S_{\boldsymbol{x}}$ satisfies an elliptic partial differential equation [18], with mixed boundary conditions given by

$$\begin{aligned} \Delta q_\delta &= 0 \text{ on } A_\delta, \\ \frac{\partial q_\delta}{\partial n}(\boldsymbol{x}) &= 0 \text{ on } \partial\Omega_r, \\ q_\delta(\boldsymbol{x}) &= 0 \text{ on } \partial\Omega_a, \\ q_\delta(\boldsymbol{x}) &= 1 \text{ on } \partial D(\delta), \end{aligned} \tag{3.1}$$

where $\partial\Omega_a$ is the small opening located on the external boundary of Ω, $\partial\Omega_r$ is the remaining part of the external boundary, which is reflecting. In polar coordinates (r, θ), the portion of the boundary $\partial\Omega_a$ is parameterized by $|\theta - \pi| \le \varepsilon$. By using the particular geometry of the annulus A_δ, an explicit estimation of the solution can be obtained by using spectral methods, developed in the context of mixed boundary value problems [19, 20, 21]. Using the method of separation of variables, the solution q_δ of problem (3.1) has the general form

$$q_\delta(r,\theta) = \frac{a_0}{2} + \sum_{n=1}^{\infty} \Big[a_n \Big(\frac{r}{R}\Big)^n + b_n \Big(\frac{\delta}{r}\Big)^n \Big] \cos(n\theta) + \alpha \log\Big(\frac{r}{\delta}\Big). \tag{3.2}$$

We wish now to estimate the coefficients a_n and b_n. We denote $\beta = \frac{\delta}{R}$. From the boundary conditions on $\partial D(\delta)$ and on $r = R$, we get

$$\frac{a_0}{2} + \sum_{n=1}^{\infty} \Big[a_n \Big(\frac{\delta}{R}\Big)^n + b_n \Big] \cos(n\theta) = 1, \tag{3.3}$$

$$\sum_{n=1}^{\infty} n \Big[\frac{a_n}{R} - \frac{b_n}{R}\beta^n \Big] \cos(n\theta) + \frac{\alpha}{R} = 0 \quad \text{for } |\theta - \pi| > \varepsilon \tag{3.4}$$

$$1 + \sum_{n=1}^{\infty} \Big[a_n + b_n \beta^n \Big] \cos(n\theta) - \alpha \log(\beta) = 0 \quad \text{for } |\theta - \pi| \le \varepsilon. \tag{3.5}$$

Using equation (3.3), we get the following identities:

$$\begin{aligned} a_0 &= 2 \\ b_n &= -a_n \beta^n \text{ for } n \ge 1. \end{aligned}$$

Using the identities above and (3.4) and (3.5), we obtain the double series equations

$$\sum_{n=1}^{\infty} n \Big[\tfrac{a_n}{R} + \tfrac{a_n}{R}\beta^{2n} \Big] \cos(n\theta) + \tfrac{\alpha}{R} = 0, \qquad \text{for } |\theta - \pi| > \varepsilon \tag{3.6}$$

$$1 + \sum_{n=1}^{\infty} \Big[a_n - a_n \beta^{2n} \Big] \cos(n\theta) - \alpha \log(\beta) = 0, \quad \text{for } |\theta - \pi| \le \varepsilon. \tag{3.7}$$

Substituting $c_n = a_n(1+\beta^{2n})$ and $H_n = \frac{2\beta^{2n}}{1-\beta^{2n}}$ equations (3.6),(3.7) have the following form

$$\frac{c_0}{2} + \sum_{n=1}^{\infty} \frac{c_n}{1+H_n} \cos(n\theta) = 0, \quad \theta \in [\pi, \pi-\varepsilon] \tag{3.8}$$

$$\alpha + \sum_{n=1}^{\infty} n c_n \cos(n\theta) = 0, \quad \theta \in [0, \pi-\varepsilon], \tag{3.9}$$

where

$$\frac{c_0}{2} = 1 - \alpha \log(\beta). \tag{3.10}$$

The asymptotic solution of equations (3.8)-(3.9) uses the double series expansion, developed in [19, 20] and used in [9] in the context of a small opening asymptotic. In Appendix A, the general solution is given. By using these results, we have the following expression for the coefficient c_0

$$c_0 = -2\alpha\Big[2\log\frac{1}{\varepsilon} + 2\log 2 + 4\beta^2 + O(\beta^2, \varepsilon)\Big]. \tag{3.11}$$

Using equation (3.10) and (3.11), we get the expression

$$\alpha = -\frac{1}{\Big(\log(\frac{1}{\beta}) + \Big[2\log\frac{1}{\varepsilon} + 2\log 2 + 4\beta^2 + O(\beta^2, \varepsilon)\Big]\Big)}. \tag{3.12}$$

To remember that α depends on β and ε, we denote it $\alpha(\beta, \varepsilon)$. For ϵ fixed and δ small, the other coefficients are estimated by using the expression of c_n (given in the appendix) by

$$c_n = \alpha(\beta, \varepsilon)\tilde{c}_n = O(\alpha(\beta, \varepsilon)), \tag{3.13}$$

where $\tilde{c}_n$ depends only on n and

$$a_n = \frac{c_n}{1+\beta^{2n}} \sim O(\alpha(\beta, \varepsilon)) \tag{3.14}$$

$$b_n = -c_n\beta^n \sim O(\alpha(\beta, \varepsilon)\beta^n). \tag{3.15}$$

These estimates show for δ small that the leading term of q is given by :

$$q_\delta(r, \theta) = \begin{cases} 1 + \alpha(\beta, \varepsilon)\log(r/\delta) + O(\beta) & \text{for } r \sim \delta \\ \\ 1 + \alpha(\beta, \varepsilon)\log(r/\delta) + O(\alpha) & \text{for } r \sim R. \end{cases} \tag{3.16}$$

The probability $p_\delta(\boldsymbol{x})$ that $T_x^a < T_x^S$ is given by $p_\delta(\boldsymbol{x}) = 1 - q_\delta(\boldsymbol{x})$ and the average over a uniform distribution in formula (3.2) using (3.16) gives

$$\begin{aligned} m_\delta = \langle p_\delta \rangle &= \frac{\int_{A(\delta)} p_\delta(r,\theta) r dr d\theta}{\int_{A(\delta)} r dr d\theta} \\ &= -2\frac{\int_\delta^R \alpha(\beta,\varepsilon)\log(r/\delta) r dr}{R^2-\delta^2} + O(\beta) \\ &= -\alpha \log\frac{1}{\beta} + O(\beta) \qquad (3.17) \\ &= \frac{\log\frac{1}{\beta}}{\log\frac{1}{\beta} + 2\log\frac{1}{\varepsilon} + 2\ln 2} + o(1). \end{aligned}$$

In the appendix some properties of p_δ are given when δ is small, which will be useful for the next section. From expression (3.17), we obtain the following asymptotic expression for the mean and the variance of the number of bounds

$$M_b = \frac{1-m_\delta}{m_\delta} = \frac{2\log\frac{1}{\varepsilon}}{\log\frac{1}{\beta}} + O(1) \qquad (3.18)$$

$$V_b = \left(\frac{1-m_\delta}{m_\delta^2}\right) = 2\left(\frac{(\log\frac{1}{\varepsilon})(\log\frac{1}{\beta} + 2\log\frac{1}{\varepsilon} + 2\log 2)}{(\log\frac{1}{\beta})^2}\right) + O(1) \qquad (3.19)$$

These expressions are valid for $\varepsilon << 1$ fixed, but are uniform in β for $\beta << 1$.

4 Estimation of Mean First Passage Time $E\{T_{\boldsymbol{x}}^A | T_{\boldsymbol{x}}^A < T_{\boldsymbol{x}}^S\}$.

In this section, we give an asymptotic estimate of the mean time to hit $\partial\Omega_a$, denoted by $T_{\boldsymbol{x}}^A$, conditioned on the event that $\{T_{\boldsymbol{x}}^A < T_{\boldsymbol{x}}^S\}$. As described in [18], the conditional process of a Brownian motion conditioned on $\{T_{\boldsymbol{x}}^A < T_{\boldsymbol{x}}^S\}$ satisfies the following stochastic differential equation

$$dX^*(t) = 2D\frac{\nabla p_\delta(X^*(t))}{p_\delta(X^*(t))}dt + \sqrt{2D}dW. \qquad (4.1)$$

On the outer boundary $\partial D(R)$, the process X^* is reflected (resp. absorbed) exactly where X is reflected (resp. absorbed). We denote $t^A(\boldsymbol{x}) = E\{T_{\boldsymbol{x}}^A | T_{\boldsymbol{x}}^A < T_{\boldsymbol{x}}^S\}$. It satisfies Dynkin's equation [10] which here is a degenerated elliptic

partial differential equation, with mixed boundary values:

$$\begin{aligned} Dp_\delta \Delta t^A + 2D\nabla t^A \cdot \nabla p_\delta &= -p_\delta \text{ on} A_\delta, \\ \frac{\partial t^A}{\partial n}(\boldsymbol{x}) &= 0 \text{ on } \partial\Omega_r, \\ t^A(\boldsymbol{x}) &= 0 \text{ on } \partial\Omega_a, \end{aligned} \tag{4.2}$$

where $\partial\Omega_r$, $\partial\Omega_a$ are respectively the reflecting part and the absorbing part of the outer boundary. We remark that no boundary conditions are needed to be given in the inner circle $\partial D(\delta)$ because $\nabla p \cdot n = \frac{\partial p}{\partial n} > 0$ and this is exactly the Fichera conditions, discussed in [22, 23], where boundary conditions cannot be given.

4.1 Asymptotic expansion of the mean first passage time

When the radius δ of the inner circle is small, we obtain an explicit asymptotic expansion of the mean conditional time t^A, solution of equation (4.2). We first derive an asymptotic solution by gluing two solutions: 1) when the initial point $\boldsymbol{x}$ is far from the inner-circle, the solution looks like the mean exit time when the drift term is set to zero. This solution is called the outer-solution and has been estimated in [24] with similar boundary conditions. 2) When the initial point $\boldsymbol{x}$ is chosen near the inner-circle, the solution can be approximated by a radial function. The approximation is valid in a boundary layer and has to match the radial part of the outer-solution at least C^1 .

4.2 Outer-solution

We now provide a construction of the outer-solution to equation (4.2). We start with the expansion of p, which depends on the parameter δ.

$$p_\delta(r,\theta) = 1 - \alpha(\delta,\epsilon)\phi_\delta(r,\theta). \tag{4.3}$$

By using the appendix, we obtain the following expression

$$\phi_\delta(r,\theta) = \Big(\sum_{n=1}^{\infty} \frac{\tilde{c_n}}{1+\beta^{2n}}\Big[\Big(\frac{r}{R}\Big)^n - \Big(\frac{\delta\beta}{r}\Big)^n\Big]\cos(n\theta) + \log\Big(\frac{r}{R}\Big) + 4\log(\frac{1}{\varepsilon})\Big) \tag{4.4}$$

Equation (4.2) can be written outside the boundary layer: $U_\delta = \{r | r_\delta \le r \le R\}$,

$$\begin{aligned} &D(1-\alpha(\delta,\epsilon)\phi_\delta(r,\theta))\Delta t^A - 2\alpha(\delta,\epsilon)\nabla\cdot\phi_\delta(r,\theta)\nabla t^A = -(1-\alpha(\delta,\epsilon)\phi_\delta(r,\theta)) \text{ on } U_\delta, \\ &\tfrac{\partial}{\partial n} t^A(\boldsymbol{x}) = 0 \text{ on } \partial\Omega_r, \text{ and } t^A(\boldsymbol{x}) = 0 \text{ on } \partial\Omega_a. \end{aligned} \tag{4.5}$$

We look for a regular asymptotic expansion of the solution :

$$t^A(\boldsymbol{x}) = u(\boldsymbol{x}) - \alpha(\delta,\epsilon)u_1(\boldsymbol{x}) + O(\alpha^2(\delta,\epsilon)). \tag{4.6}$$

Using expression (4.6) and the behavior of p as δ goes to zero, in the closed domain $D(R)$ (see appendix), we obtain from equation (4.5) that u satisfies

$$\begin{aligned} D\Delta u &= -1 \text{ on } D(R), \\ \frac{\partial u}{\partial n} &= 0 \text{ on } \partial\Omega_r, \\ u &= 0 \text{ on } \partial\Omega_a. \end{aligned} \tag{4.7}$$

We can now use the result of [9, 24] to compute the leading order term of u. For $\boldsymbol{x}$ that does not belong to a boundary layer near the absorbing boundary $\partial\Omega_a$, the asymptotic expansion of u is given by

$$u(\boldsymbol{x}) = \frac{R^2}{D}\big(\ln(\frac{1}{\varepsilon}) + \ln 2\big) + O(\varepsilon) \text{ on } U_\delta. \tag{4.8}$$

We conclude that u does not depend on the variable r and θ at the first order in δ and ϵ. Because u is a solution of equation (4.7), outside a boundary layer of $\partial\Omega_a$, the derivatives $\frac{\partial u}{\partial r}$ and $\frac{\partial u}{r\partial\theta}$ are small at the first order in δ and ϵ. We now consider the first order term in α in equation (4.5), which satisfies the equation

$$\begin{gathered} D\Delta u_1 - 2\nabla\phi\nabla u = 0 \\ \tfrac{\partial u_1}{\partial n}(\boldsymbol{x}) = 0 \text{ on } \partial\Omega_r, \text{ and } u_1(\boldsymbol{x}) = 0 \text{ on } \partial\Omega_a. \end{gathered}$$

Outside the boundary layer near $\partial\Omega_a$, the leading order term is given by $u_1(\boldsymbol{x}) = o(1)$ (for the variable δ). We get that

$$\begin{aligned} t^A(\boldsymbol{x}) &= u(\boldsymbol{x}) + o(\alpha(\delta,\epsilon)) \text{ on } U_\delta \\ &= \frac{R^2}{D}\big(\ln(\frac{1}{\varepsilon}) + \ln 2\big) + o(\alpha(\delta,\epsilon)) \text{ on } U_\delta. \end{aligned} \tag{4.9}$$

4.3 Asymptotic solution inside the boundary layer

We now provide an asymptotic expansion of the mean time t^A inside the boundary layer $BL_\delta = \{\delta < r < r_\delta\}$, where $r_\delta = \delta(1 - \frac{1}{\alpha(\delta,\epsilon)})$. The size of the boundary layer is given by formula (6.19) in the appendix. To estimate t^A, we use the expression of the conditional probability p_δ. As described in the appendix (6.2.2), it can be approximated by a radial function, so that equation (4.2) becomes

$$D\left((t^A)'' + \frac{1}{r}(t^A)'\right) + \frac{2D}{p_\delta}(t^A)'\frac{\partial p_\delta}{\partial r} = -1 \text{ on } BL_\delta, \tag{4.10}$$

and the function τ has to be glued continuously at $r = r_\delta$, using that

$$p_\delta(r,\theta) = -\frac{\alpha(\beta,\varepsilon)}{\delta}\Big(r-\delta\Big) + \alpha(\beta,\varepsilon)O\Big(r-\delta\Big). \tag{4.11}$$

The leading order term is

$$\frac{2D}{p_\delta}\frac{\partial p_\delta}{\partial r} = \frac{2D}{r-\delta}, \tag{4.12}$$

we have

$$D((t^A)'' + \frac{1}{r}(t^A)' + 2\frac{1}{r-\delta}(t^A)') \;\; = \;\; -1 \text{ on } BL_\delta. \tag{4.13}$$

The solution is given for $r > \delta$ by

$$(t^A)'(\boldsymbol{x}) = \frac{1}{r(r-\delta)^2}\left(C - \frac{1}{D}(\frac{r^2\delta^2}{2} - 2\delta\frac{r^3}{3} + \frac{r^4}{4})\right) \tag{4.14}$$

where the constant is chosen such that the function t^A is integrable. Thus the numerator vanishes for $r = \delta$. Actually $r = \delta$ has to be a third order zero of the numerator and

$$(t^A)'(\boldsymbol{x}) = -\frac{r-\delta}{4Dr}\left(r + \delta/3\right). \tag{4.15}$$

Thus,

$$t^A(\boldsymbol{x}) = -\frac{1}{4D}\left(\frac{r^2}{2} - \frac{2r\delta}{3} - \frac{\delta^2}{3}\ln(r) + C\right), \tag{4.16}$$

where the constant C is determined by the matching condition:

$$t^A(r_\delta) = \frac{R^2}{D}\big(\ln(\frac{1}{\varepsilon}) + \ln 2\big) + O(\alpha^2(\delta,\epsilon)). \tag{4.17}$$

We get

$$C \approx -4R^2\left(\ln(\frac{1}{\varepsilon}) + \ln 2\right) - \frac{\delta^2}{2\alpha^2}, \tag{4.18}$$

and for $\boldsymbol{x} \in BL_\delta$,

$$t^A(\boldsymbol{x}) \;\; = \;\; \frac{1}{D}\left(R^2\left(\ln(\frac{1}{\varepsilon}) + \ln 2\right) + \frac{\delta^2}{8\alpha^2} - \frac{r^2}{8} + \frac{r\delta}{6} + \frac{\delta^2}{12}\ln(r)\right). \tag{4.19}$$

4.4 Asymptotic estimate of the average Mean time $\langle\tau\rangle$

We now compute asymptotically the mean time $\langle\tau\rangle$ defined in equation (2.10) by

$$\langle\tau\rangle = \frac{\int_{A_\delta} t^A(\boldsymbol{x})p_\delta(\boldsymbol{x})d\boldsymbol{x}}{\int_{A_\delta} p_\delta(\boldsymbol{y})d\boldsymbol{y}} = \frac{\langle\tau\rangle_{A_\delta}}{m_\delta}, \tag{4.20}$$

where we recall that $\langle\tau\rangle_{A_\delta} = \frac{1}{Vol(A_\delta)}\int_{A_\delta} t^A(\boldsymbol{x})p_\delta(\boldsymbol{x})d\boldsymbol{x}$. $Vol(A_\delta) = \pi(R^2-\delta^2)$. To compute $\langle\tau\rangle_{A_\delta}$, we decompose the domain $A_\delta = BL_\delta \cup (A_\delta - BL_\delta)$. Using the previous computations for the outer solution (4.9) and the boundary layer solution (4.19), we compute each term separately and we get:

$$\langle\tau\rangle_{A_\delta} = m_\delta\frac{R^2}{D}\big(\ln(\frac{1}{\varepsilon}) + \ln 2\big) + \frac{R^2\beta^4}{9\alpha^2 D} + \frac{R^2}{8D(-\alpha)^3}\ln(\frac{-1}{\alpha})R^2\beta^4 + \frac{-\delta^2\alpha}{12DR^2}\ln(\frac{-\delta}{\alpha})\ln(\frac{-1}{\alpha}).$$

By taking into account the leading order term only, using the expressions of m_δ and p, we obtain after some computations that

$$\langle\tau\rangle \approx \frac{R^2}{D}\big(\ln(\frac{1}{\varepsilon}) + \ln 2\big) - \frac{R^2}{8D}\ln(\ln(\frac{1}{\beta}))\ln^3(\frac{1}{\beta})\beta^4. \tag{4.21}$$

We conclude that the boundary layer has very little influence on the leading order term at the order α.

4.5 Computation of the mean time $\langle T\rangle$ for a molecule to hit the boundary $\partial D(\delta)$ before exit

We now provide an estimate of mean time it takes for a Brownian molecule to enter into the binding site domain $D(\delta)$, before exit. To estimate the mean time $\langle T\rangle$, we observe that $E\{T^S_{\boldsymbol{x}}|T^S_{\boldsymbol{x}} < T^A_{\boldsymbol{x}}\}q_\delta(\boldsymbol{x}) + E\{T^A_{\boldsymbol{x}}|T^A_{\boldsymbol{x}} < T^S_{\boldsymbol{x}}\}p_\delta(\boldsymbol{x})$ is the mean time it takes for a Brownian molecule to exit the domain Ω when it can either be absorbed in the inner disk or in the small absorbing boundary on the outer circle. If we denote the mean time by

$$w(\boldsymbol{x}) = E\{T^S_{\boldsymbol{x}}|T^S_{\boldsymbol{x}} < T^A_{\boldsymbol{x}}\}q_\delta(\boldsymbol{x}) + E\{T^A_{\boldsymbol{x}}|T^A_{\boldsymbol{x}} < T^S_{\boldsymbol{x}}\}p_\delta(\boldsymbol{x}) \tag{4.22}$$

then w satisfies the following PDE [10],

$$\begin{aligned} \Delta w &= -\frac{1}{D} \text{ in } \Omega \\ w &= 0 \quad \text{on } \partial\Omega_a \cup \partial\Omega_\delta \\ \frac{\partial w}{\partial n} &= 0 \quad \text{on } \partial\Omega_r \end{aligned}$$

We substitute $w(r,\theta) = v(r,\theta) + \frac{R^2-r^2}{4D}$, and solve the problem for v, solution of

$$\begin{aligned} \Delta v &= 0 && \text{in } \Omega \\ v &= 0 && \text{on } \partial\Omega_a \\ \frac{\partial v}{\partial n} &= \tfrac{R}{2D} && \text{on } \partial\Omega_r \\ v &= -\tfrac{R^2-\delta^2}{4D} && \text{on } \partial\Omega_\delta. \end{aligned}$$

We proceed as in the previous section by expanding v in Fourier Series

$$v(r,\theta) = \frac{a_0}{2} + \sum_{n=1}^{\infty} \left[a_n \Big(\frac{r}{R}\Big)^n + b_n \Big(\frac{R}{r}\Big)^n \right] \cos(n\theta) + \gamma \log\Big(\frac{r}{R}\Big). \quad (4.23)$$

In a similar way as we estimated p and q (described in appendix A), from the boundary conditions on Ω_δ we get

$$\frac{a_0}{2} + \sum_{n=1}^{\infty} \left(a_n \beta^n + b_n \left(\frac{1}{\beta}\right)^n \right) \cos(n\theta) + \gamma \log\beta = -\frac{R^2-\delta^2}{4D}, \quad (4.24)$$

from which we get

$$\begin{aligned} a_0 &= -\frac{R^2-\delta^2}{2D} - 2\gamma\log\beta \quad (4.25) \\ -a_n\beta^{2n} &= b_n. \end{aligned}$$

With the definitions $c_0 = a_0$, $c_n = a_n(1-\beta^{2n})$, $H_n = \frac{2\beta^{2n}}{1-\beta^{2n}}$ the boundary conditions on $\partial\Omega_r$,$\partial\Omega_a$ have the form of double series equations

$$\begin{aligned} \frac{c_0}{2} + \sum_{n=1}^{\infty} \frac{c_n}{1+H_n} \cos(n\theta) &= 0, && \theta \in [\pi-\varepsilon, \pi] \\ \sum_{n=1}^{\infty} n c_n \cos(n\theta) &= \left(\tfrac{R^2}{2D} - \gamma\right), && \theta \in [0, \pi-\varepsilon]. \end{aligned}$$

The solution of these equations follows the steps described in the appendix and the asymptotic approximation of the coefficient c_0 is given by

$$c_0 = 2\left(\frac{R^2}{2D} - \gamma\right)\left(2\log\frac{1}{\varepsilon} + 2\log 2 + O(\beta^2)\right). \quad (4.26)$$

Using the last equation and (4.25) we obtain an equation for γ

$$-\frac{R^2-\delta^2}{2D} - 2\gamma\log\beta = 2\left(\frac{R^2}{2D} - \gamma\right)\left(2\log\frac{1}{\varepsilon} + 2\log 2 + O(\beta^2, \varepsilon)\right),$$

which gives that

$$\gamma = \frac{R^2}{2D} \frac{4\log\frac{1}{\varepsilon} + 4\log 2 + 1 + O(\beta^2, \varepsilon)}{2\log\frac{1}{\beta} + 4\log\frac{1}{\varepsilon} + 4\log 2 + O(\beta^2)}, \tag{4.27}$$

and

$$c_0 = \frac{R^2}{D} \frac{(2\log\frac{1}{\beta} - 1)(2\log\frac{1}{\varepsilon} + 2\ln 2)}{2\log\frac{1}{\beta} + 4\log\frac{1}{\varepsilon} + 4\log 2 + O(\beta^2)}. \tag{4.28}$$

Remarks

Averaging w with respect to a uniform distribution

$$\begin{aligned}
\langle w \rangle &= \frac{1}{\mathrm{Vol}(A_\delta)} \int_0^{2\pi} \int_\delta^R w(r,\theta) r dr d\theta \\
&= \frac{1}{\mathrm{Vol}(A_\delta)} 2\pi \int_\delta^R \left(v(r,\theta) + \frac{R^2 - r^2}{4D} \right) r dr = \frac{c_0 - \gamma}{2} + \frac{R^2}{8D} \\
&= \frac{R^2}{2D} \left(\frac{(2\log\frac{1}{\beta} - 1)(\log\frac{1}{\varepsilon} + \log 2) - \frac{1}{2}\log\frac{1}{\varepsilon} - \frac{1}{2}\log 2 + \frac{1}{4}\log\frac{1}{\beta} - \frac{1}{4} + O(\beta^2, \varepsilon)}{\log\frac{1}{\beta} + 2\log\frac{1}{\varepsilon} + 2\log 2 + O(\beta^2)} \right).
\end{aligned}$$

When $\beta \to 0$, we obtain the mean time to exit for only one small hole located on the boundary of the domain: this result agrees with the result obtained in ([24], eq.(1.3)). In the limit $\delta << \varepsilon$, we have the following approximation for $\langle w \rangle$,

$$\langle w \rangle \approx \frac{R^2}{D} \{ (\log \frac{1}{\varepsilon} + \log 2) + \frac{1}{8} \}, \tag{4.29}$$

while for $\varepsilon << \delta$, we have

$$\langle w \rangle \approx \frac{R^2}{2D} \{ (\log \frac{1}{\beta} - \frac{1}{2}) - \frac{1}{4} \}. \tag{4.30}$$

Final computations

To compute $E(\tau_D)$ it is sufficient to estimate the average $q(\boldsymbol{x}) E\{T_x^S | T_{\boldsymbol{x}}^S < T_{\boldsymbol{x}}^A\}$ defined by equation (2.11)

$$\langle T \rangle = \frac{\int_{A_\delta} E\{T_{\boldsymbol{x}}^S | T_{\boldsymbol{x}}^S < T_{\boldsymbol{x}}^A\} q(\boldsymbol{x}) d\boldsymbol{x}}{\int_{A_\delta} q(\boldsymbol{y}) d\boldsymbol{y}}. \tag{4.31}$$

Starting from equation (4.22), we get

$$q_\delta(\boldsymbol{x}) t^S(\boldsymbol{x}) = w(\boldsymbol{x}) - p_\delta(\boldsymbol{x}) t^A(\boldsymbol{x}),$$

thus,

$$\langle T\rangle = \frac{\int_{A_\delta} t^S(\boldsymbol{x})q_\delta(\boldsymbol{x})d\boldsymbol{x}}{|A_\delta|(1-m_\delta)} = \frac{\langle w\rangle}{1-m_\delta} - \langle\tau\rangle\frac{m_\delta}{1-m_\delta}. \tag{4.32}$$

Using expression (3.17), we have

$$\frac{1}{|A_\delta|}\int_{A_\delta} q_\delta(\boldsymbol{y})d\boldsymbol{y} = 1-m_\delta = \frac{2\ln(\frac{1}{\epsilon})+2\ln 2}{\ln(\frac{1}{\beta})+2\ln(\frac{1}{\epsilon})+2\ln 2} + O(1). \tag{4.33}$$

Finally, the expression of $\langle T\rangle$ can be computed from (4.29) and (4.21) and in the limit $\delta << \varepsilon$, the leading order term is

$$\langle T\rangle \approx \frac{R^2}{16D(\log\frac{1}{\varepsilon}+\ln 2)}\{\log\frac{1}{\beta}\} \text{ for } \delta << \varepsilon. \tag{4.34}$$

To derive the final expression for the Dwell time, we gather the computational results: using equation (2.13), we have

$$\frac{1-m_\delta}{m_\delta} \approx \frac{2\ln(\frac{1}{\epsilon})+2\ln 2}{\ln(\frac{1}{\beta})}. \tag{4.35}$$

Finally, we obtain from equation (2.12) that the dwell time in the approximation $\delta << \varepsilon$,

$$\begin{aligned} E(\tau_D) &= \langle\tau\rangle + \frac{1-m_\delta}{m_\delta}(\langle T\rangle + \frac{1}{k_{-1}}) \\ &\approx \frac{R^2}{D}(\ln(\frac{1}{\varepsilon})+\ln 2) + \frac{2\ln(\frac{1}{\epsilon})+2\ln 2}{\ln(\frac{1}{\beta})}\left(\frac{1}{k_{-1}} + \frac{R^2}{16D(\log\frac{1}{\varepsilon}+\ln 2)}\{\log\frac{1}{\beta}\}\right) + o(1). \end{aligned} \tag{4.36}$$

The expression of $E(\tau_D)$ when $\epsilon << \delta$ is more delicate and involves a different boundary layer analysis than the one given in the appendix.

5 Discussion and conclusion

In this article, we have computed the mean time spent by a molecule inside a microdomain Ω, when it can interact with some binding sites, represented as a connected sub-domain $D(\delta) \subset \Omega$. This simplified assumption ignores the scattered distribution of the binding sites but leaves one free parameter δ. A rational way to choose the radius δ is to equal the length $2\pi\delta$ with the sum of the potential well boundary length of each binding site.

More generally, the problem of estimating the Dwell time of a molecule in Ω when there are already many other independent molecules, is much more involved. The reason is that even if these molecules are not interacting, they are coupled through the competition for the binding sites. However, if the mean number of bound receptors is fixed and the variance is small enough, the Dwell time formula (4.36) can be applied, by choosing for δ, a value that is related to the amount of free binding sites available (see below). In general, when the number of bounded molecules is fluctuating, a different model is needed to account for the fluctuations. In that case, a different derivation of the Dwell time is needed.

5.1 Receptor trafficking at synapses

The explicit expression of the Dwell time can be used to describe receptor dynamics at synapses. A synapse is a micro-contact between two neurons, involved in signal transmission. In the past decades experimental observations have revealed that the molecular composition of the postsynaptic part of a synapse depends on the history of the neuronal activity [13, 12, 25, 14, 17, 15, 26]. Although it is a difficult problem to predict the chemical organization of a synapse, it has been found experimentally that the type and the number of receptors do not appear randomly, but are well regulated during specific synaptic plasticity protocols, such as Long Term Potentiation (LTP). During LTP [13], the number and the type of receptors can change, whereas extra-synaptic receptors diffuse inside a specific microdomain called the postsynaptic density (PSD). Recently, the concept has emerged that receptors are constantly moving on the neuronal surface, in and out of the synaptic domain [15]. Moreover, receptors are also cycling between the cell surface and intracellular pools. According to some recent experimental results [14], the movement of the receptors at synapses can be approximated by a random walk in the heterogeneous PSD. Moreover, it has been observed that receptors can become confined for random times [14] and can also be bound to scaffolding molecules. The PSD delimits a bounded domain Ω containing small openings at the boundary, where receptors can be exchanged with the rest of the dendrite. The PSD contains many fundamental molecules, scaffolding proteins, receptors, kinases, and many others required for the normal synaptic activity. The PSD is thus a place where the synaptic molecular machinery is concentrated. Scaffolding molecules may be used to anchor receptors and/or to change the biophysical properties of receptors. Because scaffolding molecules are scattered inside the domain Ω, in the present model we have replaced the complex organization of the PSD by a homogenized domain (Figure 1). We can apply the result of the first part of the present paper to obtain some estimates of the mean time spent by a receptor inside the PSD, when it can bind with scaffolding molecules. Estimate (4.36)

of the Dwell time $E(\tau_D)$ depends on the size δ of the scaffolding domain and is a good approximation when the amount of free scaffolding molecules is small $\delta << 1$ and when the corral barrier, measured by ε, made by the impenetrable molecules around the PSD, is also small.

5.2 Dwell time of a single receptor in a synapse containing many other receptors

To estimate the mean time a receptor stays inside the PSD, we consider the case where the influx J of receptors entering the PSD is fixed. The Dwell time can be computed from formula (4.36) once the value of the radius δ is known. δ is indeed the radius of the disk containing the free scaffolding molecules. To obtain an estimate of δ, we consider the dynamics where each injected receptor can escape with a rate τ, approximated by formula (1.1). When the number of injected receptors is balanced by the exiting one from the PSD, the total number of free receptors inside the PSD is given by

$$[R] = J\tau. \tag{5.1}$$

(for a detailed analysis see [27]). Under the steady state assumption, the number of free scaffolding molecules can be estimated by using the law of chemical reaction (1.10) which says that

$$K = \frac{[R-S]}{[R][S]}, \tag{5.2}$$

where $[R-S]$ is the number of bounds. $[R]$ (resp. $[S]$) the number of free receptors (resp. scaffolding molecules) K is the equilibrium reaction constant per unit area. If $[S_0]$ denotes the initial number of scaffolding molecules, the conservation of matter (the total number of scaffolding molecules is conserved) and equation 5.2 implies that

$$\begin{aligned} [S_0] &= [S] + [R-S] = [S] + K[R][S] && (5.3)\\ &= (1 + KJ\tau)[S] && (5.4) \end{aligned}$$

Thus, if $[S]$ (resp. $[S_0]$) occupies a surface $\pi\delta^2$, (resp. $\pi\delta_0^2$), then

$$\delta = \frac{\delta_0}{\sqrt{1 + KJ\tau}}. \tag{5.5}$$

δ_0 can be related to the concentration c_0 of scaffolding molecules by $c_0 = \frac{[S_0]}{\pi\delta_0^2}$. To obtain the mean time estimate, expression (5.5) of δ should be used in the Dwell time formula.

Expression (5.5) depends on the equilibrium constant K, which in fact depends implicitly of δ. Thus to provide a more accurate value of δ, we note that the forward binding rate k_1 represents the rate of arrival of a free receptor to a free binding site and can be approximated by

$$k_1 \approx \frac{1}{\langle T \rangle}, \tag{5.6}$$

where $\langle T \rangle$ is given by equation (4.31). Using the previous considerations and the conservation law 5.3, we have

$$\begin{aligned} [S_0] &= [S] + [R - S] = [S] + K[R][S] && (5.7) \\ &= (1 + \frac{J\tau}{k_{-1}\langle T \rangle})[S], && (5.8) \end{aligned}$$

where τ is approximated by expression (1.1) and $\langle T \rangle$ (4.34) depends on δ, which is denoted by $\langle T \rangle(\delta)$. Using equation (5.5), δ is solution of equation

$$\delta = \frac{\delta_0}{\sqrt{1 + \frac{J\tau}{k_{-1}\langle T \rangle(\delta)}}}. \tag{5.9}$$

In practice, the value of δ obtained by solving equation (5.9) can now be used to estimate the Dwell time, the mean number of bounds and the other mean times.

Finally, when the total number of receptors inside Ω is small, the radius δ cannot be approximated by a constant, rather it is fluctuating and in that case, the present approach needs to be adapted. A variant model of the PSD has been proposed in [27], based on a Markovian approach, which uses an in- and out-flux of receptors. At steady state, under some approximations, some estimates of the mean and the fluctuation of the total number of bound receptors are obtained, however the computations depend on an a priori expression of the forward binding rate.

6 Appendix

6.1 Solution of double series equation

In this section we give the mathematical details needed to solve the double series equation (3.8)-(3.9). The method was already used in [24],[19]. Starting with the equations

$$\frac{c_0}{2} + \sum_{n=1}^{\infty} \frac{c_n}{1+H_n} \cos(n\theta) = 0, \quad \theta \in [\pi, \pi - \varepsilon] \tag{6.1}$$

$$\alpha + \sum_{n=1}^{\infty} n c_n \cos(n\theta) = 0, \quad \theta \in [0, \pi - \varepsilon], \tag{6.2}$$

we are interested in computing α and the coefficients $\{c_i\}$. Let us define the function $h(\theta)$ for $\theta \in [0, \pi - \varepsilon]$ by

$$\frac{c_0}{2} + \sum_{n=1}^{\infty} \frac{c_n}{1 + H_n} \cos(n\theta) = \cos(\frac{\theta}{2}) \int_{\theta}^{\pi-\varepsilon} \frac{h(t)}{\sqrt{\cos(\theta) - \cos(t)}} \tag{6.3}$$

Using this definition and the Fourier coefficient formula ([24])we can write

$$c_n = \frac{1 + H_n}{\sqrt{2}} \int_0^{\pi-\varepsilon} h(t)[P_n(\cos(t)) + P_{n-1}(\cos(t))]dt, \tag{6.4}$$

$$c_0 = \sqrt{2} \int_0^{\pi-\varepsilon} h(t)dt, \tag{6.5}$$

where Mehler's identity for Legendre polynomials gives ([19] ch.2)

$$P_n(\cos(u)) = \frac{\sqrt{2}}{\pi} \int_0^u \frac{\cos(n + \frac{1}{2})d\theta}{\sqrt{\cos(\theta) - \cos(u)}}.$$

Integrating equation (6.2), using the expression for the coefficients (6.4) into the integrated equation and the identity

$$\frac{1}{\sqrt{2}} \sum_{n=1}^{\infty} \{P_n(\cos(t)) + P_{n-1}(\cos(t))\} \sin(n\theta) = \frac{\cos(\frac{1}{2}\theta) H(\theta - t)}{\sqrt{\cos(t) - \cos(\theta)}},$$

where H is the Heaviside function, we get the integral equation

$$\int_0^{\theta} \frac{h(t)}{\sqrt{\cos(t) - \cos(\theta)}} + \int_0^{\pi-\varepsilon} K_\beta(\theta, t) h(t) dt = \frac{-\alpha\theta}{\cos(\frac{\theta}{2})}, \tag{6.6}$$

where the kernel function K_β is

$$K_\beta(\theta, s) = \frac{1}{\sqrt{2}\cos(\frac{\theta}{2})} \sum_{n=1}^{\infty} H_n(P_n(\cos(t) + P_n(\cos(t))).$$

Using the first elements in the infinite series we can give an asymptotic expansion to K_β

$$K_\beta(t, s) = 2\beta^2 \cos^2(s) \sin(t) + \mathrm{O}(\beta^4). \tag{6.7}$$

Equation (6.6) can be transformed according to the Abel transform

$$\begin{aligned} f(x) &= \int_0^x \frac{g(t)dt}{(p(x) - p(t))^q} \\ g(t) &= -\frac{\sin(\pi q)}{\pi} \frac{d}{dt} \int_0^t \frac{p'(x) f(x) dx}{(p(x) - p(t))^{1-q}}, \end{aligned}$$

where $p(x)$ is monotonic increasing function. Transforming eq.(6.6), with $q = \frac{1}{2}$ and $p(x) = -\cos(x)$ we get

$$h(\theta) - \int_0^{\pi-\varepsilon} \tilde{K}_\beta(\theta, t)h(t)dt = \frac{1}{\pi}\frac{d}{d\theta}\int_0^\theta \frac{2\alpha t \sin(\frac{1}{2}t)dt}{\sqrt{\cos t - \cos\theta)}} \tag{6.8}$$

with $\tilde{K}_\beta(t,s) = -\frac{1}{\pi}\frac{d}{dt}\int_0^t \frac{K_\beta(u,s)\sin(u))}{\sqrt{\cos(u)-\cos(t)}}$. If we define $z(\theta) = \frac{1}{\pi}\frac{d}{d\theta}\int_0^\theta \frac{2\alpha t \sin(\frac{1}{2}t)dt}{\sqrt{\cos t - \cos\theta}}$, then equation (6.6) has the form $(I - \tilde{K}_\beta)h = z$. This is the Fredholm integral equation, which can be approximated using the infinite sum

$$h = z + \tilde{K}_\beta z + \tilde{K}_\beta^2 z + \dots \tag{6.9}$$

Computing the first elements in the sum gives an approximation to $h(\theta)$ which in turn, by substituting the approximation into the expressions for c_n gives an approximation for the coefficients. To calculate c_0 up to $\mathrm{O}(\varepsilon, \beta^4)$ we have to evaluate the integral

$$\sqrt{2}\left(\int_0^{\pi-\varepsilon} z(t)dt + \int_0^{\pi-\varepsilon}\int_0^{\pi-\varepsilon} K(\tilde{s}, t)_\beta z(t)dtds\right).$$

The computation is made in [24] and gives

$$c_0 \approx 2\alpha(2\log\frac{1}{\varepsilon} + 2\log 2 + 4\beta^2).$$

6.2 Properties of the conditional probability p_δ

6.2.1 Inside A_δ

q_δ is solution of equation (3.1) and depends on the parameter δ.

Proposition 1 *The sequence p_δ converges uniformly to the constant 1, on any compact set K strictly contained in the domain A_δ. More specifically, for any $K \subset A_\delta$, there exists a constant $C > 0$ such that for all $r, \theta \in K$,*

$$\begin{aligned} |p_\delta(r,\theta) - 1| &\leq C\alpha(\beta,\varepsilon) \\ |\nabla p_\delta(r,\theta)| &\leq C\alpha(\beta,\varepsilon) \end{aligned}$$

where $\alpha(\beta,\varepsilon)$ is defined by (3.12) and

$$0 < \alpha(\beta,\varepsilon) = \alpha(\frac{\delta}{R},\varepsilon) \leq \frac{C}{\ln(\frac{1}{\delta})} \tag{6.10}$$

which tends to zero when δ goes to zero.

Proof. To estimate p_δ we consider expression (3.2), which can be written as

$$-p_\delta = q_\delta(r,\theta) - 1 = \sum_{n=1}^{\infty} \frac{c_n}{1+\beta^{2n}} \Big[\Big(\frac{r}{R}\Big)^n - \Big(\frac{\delta\beta}{r}\Big)^n \Big] \cos(n\theta) + \alpha(\beta,\varepsilon) \log\Big(\frac{r}{\delta}\Big).$$

where $\alpha(\beta,\varepsilon)$ is given by expression (3.12) and we recall that

$$c_n \;\; = \frac{1+H_n}{\sqrt{2}} \int_0^{\pi-\varepsilon} h(t) P_n(\cos(t)) + P_{n-1}(\cos(t))]dt. \tag{6.11}$$

By definition $H_n = O(\beta^{2n})$ and P_n is the Legendre polynomial. For $x \in [-1,1]$ and all n, $|P_n(x)| \leq 1$. Moreover, using formula (6.9), we obtain that

$$h(t) = z(t) + O(\beta^2) = -\frac{2\alpha}{\pi} \frac{d}{dt} \int_0^t \frac{u \sin u}{\sqrt{\cos u - \cos t}} du. \tag{6.12}$$

Thus we conclude from the explicit formula (6.11) that there exists a constant $C > 0$ such that for all n

$$|c_n| \leq C\alpha(\beta,\varepsilon) \tag{6.13}$$

which is independent of n. We denote $c_n = \tilde{c_n}\alpha(\beta,\varepsilon)$. We can now obtain the desired estimates. For $r_0 < r < R_1 < R$, we get,

$$1 - p_\delta(r,\theta) = 1 + \alpha(\beta,\varepsilon)\Big(\sum_{n=1}^{\infty} \frac{\tilde{c_n}}{1+\beta^{2n}} \Big[\Big(\frac{r}{R}\Big)^n - \Big(\frac{\delta\beta}{r}\Big)^n \Big] \cos(n\theta) + \log\Big(\frac{r}{\delta}\Big)\Big) \tag{6.14}$$

Thus,

$$|1 - p_\delta(r,\theta)| \leq I + II, \tag{6.15}$$

where

$$I \leq |1 - \alpha(\beta,\varepsilon) \log\Big(\frac{R_1}{\delta}\Big)| \leq C \frac{\ln(R_1/r_0) + O(1)}{\ln(R/\delta) + O(1)} \tag{6.16}$$

$$II \leq \alpha(\beta,\varepsilon) \sum_{n=1}^{\infty} \Big[\Big(\frac{R_1}{R}\Big)^n + \Big(\frac{\delta\beta}{r_0}\Big)^n \Big] \leq C\alpha(\beta,\varepsilon). \tag{6.17}$$

The last part of these inequalities uses the asymptotic expression of α given by formula (3.12). These inequalities show that on any compact set of A_δ, $1 - p_\delta$ converges uniformly to zero at a rate $\frac{1}{\ln(1/\delta)}$. Similarly, to estimate the gradient we estimate separately $|\frac{\partial p}{\partial r}|$ and $|\frac{1}{r}\frac{\partial p}{\partial \theta}|$. First,

$$-\frac{\partial p_\delta}{\partial r}(r,\theta) = \alpha(\beta,\varepsilon)\Big(\sum_{n=1}^{\infty} \frac{n\tilde{c_n}}{1+\beta^{2n}} \Big[\Big(\frac{r^{n-1}}{R^n}\Big) + \Big(\frac{(\delta\beta)^n}{r^{n+1}}\Big) \Big] \cos(n\theta) + \frac{1}{r}\Big),$$

we get

$$|\frac{\partial p_\delta}{\partial r}(r,\theta)| \leq |\alpha(\beta,\varepsilon)|\Big(\sum_{n=1}^{\infty} n\Big[\Big(\frac{R_1^{n-1}}{R^n}\Big) + \Big(\frac{(\delta\beta)^n}{r_o^{n+1}}\Big)\Big] + \frac{1}{r_0}\Big) \leq C|\alpha(\beta,\varepsilon)|$$

and second,

$$\frac{1}{r}\frac{\partial p_\delta}{\partial \theta}(r,\theta) = \frac{\alpha(\beta,\varepsilon)}{r}\Big(\sum_{n=1}^{\infty} \frac{\tilde{c_n}}{1+\beta^{2n}}\Big[\Big(\frac{r}{R}\Big)^n - \Big(\frac{\delta\beta}{r}\Big)^n\Big] n\sin(n\theta)\Big)$$

and

$$|\frac{1}{r}\frac{\partial p}{\partial \theta}| \leq |\frac{\alpha(\beta,\varepsilon)}{r_0}|\Big(\sum_{n=1}^{\infty}\Big[\Big(\frac{R_1}{R}\Big)^n + \Big(\frac{\delta\beta}{r_0}\Big)^n\Big] n\Big) \leq C|\alpha(\beta,\varepsilon)|.$$

∎

6.2.2 The boundary layer

We consider now the behavior of p_δ near the the inner circle $r = \delta$, where p_δ vanishes. We expect to see a boundary layer near the circle $r = \delta$, as δ goes to zero. p_δ is a regular function and a Taylor expansion in the r-variable inside expression (6.14) gives that

$$-p_\delta(r,\theta) = \frac{\alpha(\beta,\varepsilon)}{\delta}\Big(r-\delta\Big) + \alpha(\beta,\varepsilon)\sum_{n=1}^{\infty} n\frac{\tilde{c_n}}{1+\beta^{2n}}\Big[2R\beta^{n-1}\Big]\cos(n\theta)\Big(r-\delta\Big) + O\Big(r-\delta\Big)^2.$$

The leading order term is radial and we get

$$p_\delta(r,\theta) = -\frac{\alpha(\beta,\varepsilon)}{\delta}\Big(r-\delta\Big) + \alpha(\beta,\varepsilon)O\Big(r-\delta\Big). \tag{6.18}$$

To estimate the size of the boundary layer, we look at the value r_δ such that p_δ is of the order one. Using the previous approximation of p_δ (6.18) we get

$$\begin{aligned} r_\delta &= \delta - \frac{\delta}{\alpha(\beta,\varepsilon)} && (6.19)\\ &= \delta + \delta(\ln\frac{1}{\delta} + 2\ln\frac{1}{\varepsilon} + 2\ln 2 + \ln R + O(\beta^2)). && (6.20)\end{aligned}$$

6.2.3 Convergence of p_δ in the neighborhood of $\partial D(R)$

The sequence of harmonic function p_δ converges uniformly on any compact set of $D(R) - \{0\}$ to the function 1. We show now that this is also the case in the neighborhood of $\partial D(R)$. We use the elliptic estimates given in [28] derived

at the boundary. We can also directly extend as a harmonic function p_δ to a neighborhood T of $D(R)$. We have that

$$\sup_{\{x \in K\}} |\nabla p_\delta| \leq C \tag{6.21}$$

for any compact K in T. By Ascoli's theorem, there exists a subsequence of p_δ converging in $C^{0,\alpha}$. We conclude since p_δ converges to 1 on any compact set of $D(R) - \{0\}$ that the sequence p_δ converges to 1 on $T - \{0\}$ and is a weak solution of

$$\begin{aligned} \Delta u &= 0 \text{ on } D(R) - 0 \\ u(x) &= 1 \text{ on } \partial\Omega_a, \\ \frac{\partial u}{\partial n}(x) &= \text{ on } \partial D(\delta), \end{aligned} \tag{6.22}$$

Because $0 \leq u \leq 1$, the solution can be extended up to 0 and the only solution of equation (6.22) is the constant 1. We conclude that the sequence p_δ converges to the constant one uniformly on $\overline{D(R)}$.

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